FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

ANADA 200-027

ANADA/Generic Sponsor:

Planalquimica Industrial Ltda
Rua das Magnólias nr. 2405
Jardim das Bandeiras
CEP 13053-120
Campinas - Sao Paulo - Brazil

a.	Established Name:	Nicarbazin
b.	Trade/Proprietary Name:	NICARMIX (nicarbazin) 25%
c.	Dosage Form:	Type A medicated article
d.	How Supplied:	25 kg (55.12 lb) multiwalled bags
e.	How Dispensed:	OTC
f.	Amount of Active Ingredient:	Type A - 113.5 g/lb (25%) Type C - 113.5 g/ton (0.0125%)
g.	Route of Administration:	This drug is administered orally by adding the Type A medicated article to make a complete feed (Type C medicated feed).
h.	Species:	Chickens (except laying hens)
i.	Pioneer Product/ "Listed Product"	NICARB® (nicarbazin) 25% (Merck, NADA 09-476)

2. INDICATIONS:

As an aid in preventing outbreaks of cecal (*Eimeria tenella*) and intestinal (*E. acervulina, E. maxima, E. necatrix* and *E. brunetti*) coccidiosis in chickens.

3. DOSAGE:

113.5 g/ton of Type C medicated feed is to be fed as the only ration from the time the chicks are placed on litter until past the time when coccidiosis is ordinarily a hazard.

4. TARGET ANIMAL SAFETY and DRUG EFFECTIVENESS:

A. PIVOTAL STUDY:

1) Type of Study: Clinical end point bioequivalence study (broilers) - Experiment GPR-890302

Test Product: NICARMIX (nicarbazin) 25% Type A medicated article (Planalquimica)

Reference Product: NICARB® (nicarbazin) 25% Type A medicated article (Merck)

2) Investigator: Larry R. McDougald, Ph.D.
Director of Research
Georgia Poultry Research, Inc.
P.O. Box 5822
Athens, Georgia 30604

Statistician: Larry R. McDougald, Ph.D.
Department of Poultry Science
University of Georgia
Athens, Georgia 30602

3) General Design of Investigation:

a) Purpose of Study:

To compare the efficacy of nicarbazin manufactured by Planalquimica to that of nicarbazin sold by Merck in broiler chickens infected with *E. tenella*.

b) Test Animals:

Broiler pullets (female) Peterson X Arbor Acres obtained from Seaboard Farms Hatchery, Athens, Georgia. Six hundred birds were used for the study. They were randomized into cages of 10 birds at 12 days of age (15 replicate cages).

c) Treatments:

1. Uninfected, unmedicated
2. Infected, unmedicated
3. Infected, nicarbazin Planalquimica
4. Infected, nicarbazin Merck

A standard broiler mash was used in all treatments. Feed mixtures were assayed for drug content.

d) Dosage Form:

Type A medicated articles.

e) Route of Administration and Dosage:

Both drugs were administered orally in the feed at a rate of 113.5 g/ton for the duration of the trial.

f) Test Duration:

The trial started April 18, 1989 and ended April 26, 1989 (8 days). The birds were given designated treatments (Day -2) and infected at the age of 2 weeks (Day 0) with a culture of a recent field isolate of 100,000 *E. tenella* oocysts (FS 284, Virginia, 1988) administered orally. Six days (Day 6) later the experiment was terminated.

g) Pertinent Parameters Measured:

Mortality, cecal lesion scores, and average weight gain were the parameters measured.

4) Results:

Table 1. Comparison of the efficacy of nicarbazin from two sources against *Eimeria tenella*. Summary of weight gains, mortality and cecal lesion scores. (Experiment GPR-890302)

Treatment[1]	Percent Mortality	Average Gain(g/bird)[2]	Average Cecal Lesion Score[3]
Unmedicated, Uninfected Controls	0.0	205	0.00
Unmedicated, Infected Controls	8.0	149	3.49
Nicarbazin (0.0125%) (Planalquimica)	0.0	193	0.12
Nicarbazin (0.0125%) (Merck)	0.0	195	0.01

[1]Replicated in 15 cages of 10 birds each.

[2]Average gain per survivor (g) from the time of inoculation (DO), to 6 days postinoculation (D+6).

[3]Average cecal lesion scores based on the average of 5 birds per cage. Lesions were scored according to Johnson and Reid, 1970. Experimental Parasitology 28, 30-36.

5) Conclusion:

The results demonstrated no difference in the efficacy of nicarbazin Planalquimica and nicarbazin Merck against a recent field isolate of E. tenella in broiler chickens.

B. PIVOTAL STUDY:

1) Type of Study: Clinical end point bioequivalence study (broilers) - Experiment GPR-881110

   Test Product: NICARMIX (nicarbazin) 25% Type A medicated article (Planalquimica)

   Reference Product: NICARB® (nicarbazin) 25% Type A medicated article (Merck)

2) Investigator: Larry R. McDougald, Ph.D.
   Director of Research
   Georgia Poultry Research, Inc.
   P.O. Box 5822
   Athens, Georgia 30604

   Statistician: Larry R. McDougald, Ph.D.
   Department of Poultry Science
   University of Georgia
   Athens, Georgia 30602

3) General Design of Investigation:

   a) Purpose of Study:

      To compare the efficacy of nicarbazin manufactured by Planalquimica to that of nicarbazin sold by Merck in broiler chickens infected with *E. acervulina*.

   b) Test Animals:

      One day old broiler cockerels (male) Peterson X Arbor Acres obtained from Seaboard Farms Hatchery, Athens, Georgia. Six hundred birds were used for the study. They were randomized into cages of 10 birds at 12 days of age (15 replicate cages).

   c) Treatments:

      1. Uninfected, unmedicated
      2. Infected, unmedicated
      3. Infected, nicarbazin Planalquimica
      4. Infected, nicarbazin Merck

      A standard broiler mash was used in all treatments. Feed mixtures were assayed for drug content.

   d) Dosage Form:

      Type A medicated articles.

e) Route of Administration and Dosage:

Both drugs were administered orally in the feed at a rate of 113.5 g/ton for the duration of the trial.

f) Test Duration:

The trial started June 25, 1989 and ended July 2, 1989 (8 days). The birds were given designated treatments (Day -2) and infected at the age of 2 weeks (Day 0) with a culture of a recent field isolate of 1,000,000 *E. acervulina* oocysts (FS 284, Virginia, 1988) administered orally. Six days (Day 6) later the experiment was terminated.

g) Pertinent Parameters Measured:

Mortality, cecal lesion scores, and average weight gain were the parameters measured.

4) Results:

Table 2. Comparison of the efficacy of nicarbazin from two sources against *Eimeria acervulina*. Summary of weight gains, mortality and cecal lesion scores. (Experiment GPR-881110)

Treatment[1]	Percent Mortality	Average Gain (g/bird)[2]	Average Intestinal Lesion Score[3]
Unmedicated, Uninfected Controls	0.0	193	0.00
Unmedicated, Infected Controls	0.0	78	3.91
Nicarbazin (0.0125%) (Planalquímica)	0.0	155	0.76
Nicarbazin (0.0125%) (Merck)	0.0	152	0.79

[1]Replicated in 15 cages of 10 birds each.

[2]Average gain per survivor (g) from the time of inoculation (DO), to 6 days postinoculation (D+6).

[3]Average cecal lesion scores based on the average of 5 birds per cage. Lesions were scored according to Johnson and Reid, 1970. Experimental Parasitology 28, 30-36.

5) Conclusion:

The results demonstrated no differences in the efficacy of both formulations against single infection of *E. acervulina*.

5. HUMAN FOOD SAFETY:

Tolerance

The tolerances established for the pioneer product apply to the generic product. A tolerance of 4 ppm is established for residue in uncooked chicken muscle, liver, skin, and kidney (21 CFR 556.445).

Withdrawal Period

The following study was conducted by Dr. Carey L. Quarles of Colorado Quality Research, Inc., Ft. Collins, CO, and Dr. Halina Kramer, Group Leader of Hazleton Laboratories America, Inc., Madison, WI.

Nicarbazin manufactured by Planalquimica, LTDA of Sao Paulo, Brazil was fed to broiler chickens (equal number of males and females) at a concentration of 0.0125% in the feed beginning at one day of age and continuing for 49 days. Four birds (equal number of each sex) were sacrificed at 24, 36, 48, 60, and 72 hours after removal of nicarbazin-containing feed, and tissues were collected for assay of nicarbazin residues. The sponsor used the HPLC assay that has been approved for regulatory use. The residues in muscle and skin/fat were below the accepted tolerance of 4 ppm nicarbazin (21 CFR 556.445) at all withdrawal times, and the liver residues were below the tolerance after 60 hours withdrawal.

Nicarbazin Residue Depletion in Chicken Tissue: Data Summary

ppm Nicarbazin[1] at Withdrawal Time (Hours)					
Tissue[2]	24	36	48	60	72
Liver	6.62 (±1.08)	4.53 (±0.83)	4.31 (±0.23)	3.08 (±0.27)	2.49 (±1.02)
Muscle	0.98 (±0.088)	0.61 (±0.19)	0.32 (±0.086)	0.12 (±0.065)	0.12 (±0.089)
Skin/Fat	0.88 (±0.042)	0.86 (±0.14)	0.53 (±0.081)	0.33 (±0.16)	0.19 (±0.13)

[1] Nicarbazin residue values represent an average of assays from 2 female and 2 male birds per tissue and withdrawal time.

[2] Tissues from birds receiving 0.0125% nicarbazin for 49 days, followed by unmedicated feed for the indicated withdrawal time.

A statistical analysis of the depletion data for nicarbazin in liver using the upper tolerance limit containing a 99 percentile of the population with 95% confidence limits yielded a withdrawal period of four days.

Regulatory Methods for Residues

The determinative assay for measuring residues in liver from chickens treated with nicarbazin is by high performance liquid chromatography (HPLC) with UV detection. The

regulatory method is provided in the AOAC reference: Lewis, J.L., Macy, T.D., & Garteiz, D.A. (1989) J. Assoc. Off. Anal. Chem. 72, 577-581.

6. AGENCY CONCLUSIONS:

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that nicarbazin when used under the proposed conditions of use, is safe and effective for its labeled indications.